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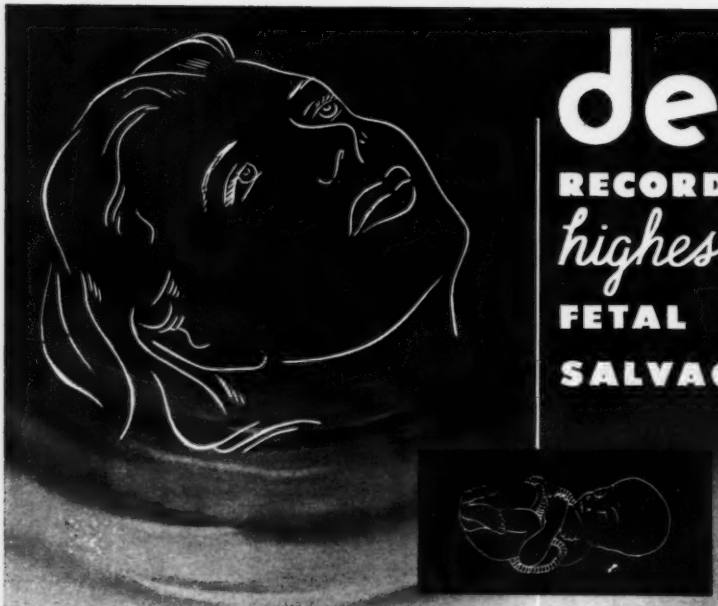

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EDITORIAL

Malpractice

FREDERIC R. STEARNS, M.D., *Editor*

The threat of a malpractice suit is constantly in the mind of every practicing physician, especially because of the fluctuations and changing boundaries of the definition of malpractice. It seems appropriate, therefore, to approach this subject again.

A particularly lucid explanation of the issues involved was presented by Mr. Emmett Good, Chief Attorney of the Veterans' Administration, New York, New York, on occasion of the first Psychosurgery Conference in 1949. Because of the legal problems which present themselves in the relatively new field of brain surgery for the management of mental diseases, Mr. Good was asked to discuss the question of malpractice in this respect. Mr. Good stated that brain surgery for mental diseases did not constitute a different problem of malpractice and he, therefore, gave a concise outline of the fundamental principles of malpractice.

Mr. Good emphasized: "A physician or surgeon by taking charge of a case impliedly represents that he possesses, and the law places upon him the duty of possessing, that degree of learning and skill as is ordinarily possessed by physicians and surgeons in the locality where he practices, and which is ordinarily regarded by those conversant with such employment as necessary to qualify him to engage in the practice of medicine and surgery."

Mr. Good stated that it is also a basic principle that, upon consenting to treat a patient, it becomes the duty of a physician or surgeon "to use reasonable care and diligence in the exercising of his skill in the application of his learning to accomplish the purpose for which he was employed." He is, of course, under the obligation to apply his best judgment in the exercising of his profession by using this knowledge.

Considering the liability, the law states that the physician and surgeon be liable for an injury to his patient "resulting from (1) want of requisite knowledge and skill; (2) the omission to exercise reasonable

care; or (3) the failure to use his best judgment." It is not required, according to the law, that a physician or surgeon possesses extraordinary learning and skill. However, he is obligated to keep abreast of any progress in his profession. In case that he does not employ approved methods and if he thus injures the patient, he may be held liable irrespective of his good intentions.

On the other hand, the law holds that "if the procedure is attended with injury to other parts, or other diseases develop for which there is no known cure, the physician is not liable." It is also a general rule that if a physician and surgeon does not adhere to an established method "he has to be prepared to take the risk of establishing by his success the propriety and the safety of his experiment." Conversely, if any discoveries have shown that a method of treatment or a surgical technic previously not used has been rendered improper, the application of these methods may be a reason for an action for malpractice. "If, however, the course of treatment or a surgical technique, at the time it was given, followed that generally used by members of the medical profession, there is a very remote chance of liability against the surgeon."

As to the exercise of reasonable care and diligence, such care and diligence include not only diagnosis and treatment but also proper instructions to the patient.

In considering the liability of the surgeon in particular, Mr. Good stated: "1. A surgeon is bound to use reasonable knowledge and care in first learning the condition of his patient. 2. In ascertaining if an operation is necessary. 3. In determining whether the time and place are proper. 4. In making the diagnosis of the case." It is interesting that Mr. Good emphasizes that a consultation with another specialist in securing the proper diagnosis would not free the surgeon of his liability if the diagnosis made was not correct.

The importance of the malpractice problem has recently been emphasized from a statistical viewpoint. Raveson, writing in May, 1950, issue of *Medical Economics*, pointed out that some 5,000 cases of malpractice are tried annually in the United States, and that thousands more are settled out of court.

NOTES on MEDICAL STATISTICS

ACCIDENTS

Preliminary figures indicate that the loss of lives from accidents in 1950 was 89,000. About 35,000 people were killed in motor vehicle accidents (40% of the total); injuries in and about the home caused approximately 27,000 deaths (about 33 percent of the total); there were about 15,000 deaths from occupational accidents; deaths in public accidents are estimated at around 13,000. There were 11 disasters in 1950 which took more than 25 lives, each; the aggregate lives lost in these accidents was in excess of 500.

I. Current Status of ACTH and Cortisone

The first of two articles on this subject. The next article will appear in November

EDGAR A. HAUNZ, M.D., M.S., (Med.),
Department of Medicine, Grand Forks Clinic, Grand Forks, North Dakota

INTRODUCTION

In the past year the widespread use of the adrenocorticotropic hormones has engendered more conservatism in evaluating both their good and bad effects. It might be said that the effects are not as permanently good or as permanently bad in the various disease states treated as previously supposed. Time and experience have contributed to wiser selection of cases and avoidance of overdosage. For example, such phenomena as hypokalemia, hypochloremic alkalosis, cerebral disturbances, cutaneous reactions, edema, hypertension, hyperglycemia, gastro-intestinal disturbances, and various features of Cushing's syndrome have been significantly reduced in severity and incidence by what might be termed clinical calibration of dosage. On the other hand, there currently is still some over-indulgence in empirical corticosteroid therapy beyond the confines of the thus-far-established therapeutic spectrum. This tendency is naturally enhanced by the availability of oral cortisone.

LIMITATIONS

It is most urgent that bifocals be applied to the scientific eye in order that potentialities, dangers and limitations of the corticosteroids thus far assessed will be in constant focus while the long-range search for therapeutic conquest continues. For example, the weight of evidence to date incriminating corticosteroid therapy as deleterious in active tuberculosis has prompted the National Tuberculosis Association to recommend that ACTH and cortisone *not be used* in such cases and that these agents be used only with extreme caution in cases in which possibly latent tuberculosis may exist. This charges the physician with a serious responsibility—to first exclude possible tuberculosis *in all* candidates for such therapy. Before instituting this expensive treatment in various disease states, a chest roentgenogram offers cheap protection.

Another example is found in the

protracted observations that ACTH and cortisone, particularly the latter, may "actually increase the severity of, or enhance the susceptability to, many infections in experimental animals and in man." This subject has been both editorialized and well reviewed in the New England Journal of Medicine during the past year.

These statements are not intended to condemn corticosteroid therapy in all infections, since it has appeared to be valuable in certain infections under certain conditions. However, there is unanimous agreement on the point that *it should not be more than adjunctive therapy with appropriately selected antibiotics,* especially in the case of bacterial infections. In essence, the role of corticosteroids in any of these situations is that of restoring the physiological process to nearly normal during the time that the patient is being treated with the specific antibiotic for the infectious process. In this way, overwhelming or fatal infection is averted and time may be gained for maximal effectiveness of the antibiotic.

DANGER OF MASKING INFECTION

Finally, it is most urgent to remember that one of the very real dangers of corticosteroid therapy lies in the capacity of these hormones to obscure the incidental development of acute infections in patients being treated for other diseases. ACTH and cortisone possess no inhibiting effect upon bacteria, although they probably "exert a polyvalent antitoxic effect, in some way protecting multiple body cells against multiple toxins."

There is no humor in the remark that either ACTH or cortisone may be a wolf in sheep's clothing in certain situations. Thus, recent case reports dramatically suggest that corticosteroid hormone therapy may not only exacerbate a preexisting peptic ulcer to the extent of acute perforation, but may concurrently mask these evil effects with a "striking picture of well-being as to color, temperature and blood pressure" in the patient. One case report demonstrates that these effects may lead to the patient's death.

At the present level of thought, at least two theories are advanced to explain the deleterious effects of ACTH on peptic ulcer. According to a theory expressed by Spiro et. al., ACTH increases excretion of pepsinogen by the gastric glands. Another theory advanced by Ragan and coworkers is based on the depression of the growth of granulations in wounds.

INTRAVENOUS ACTH

In the past year it has been shown that administration of ACTH by continuous intravenous drip effects sustained adrenal cortical stimulation in humans (Gordon) and that smaller quantities are required by this route than by the intramuscular route. Renold *et. al.* treated 100 subjects in this fashion and some interesting clinical observations were the following:

1. Over an eight-hour period, 20 mg. of ACTH causes maximal stimulation of the adrenal cortices in the average person, hence larger doses at one time appear to be unnecessary. However, prolonging the duration of the infusion increases the adrenal cortical response to a given dose.
2. A normal adrenal response was effected by intravenous ACTH in four patients who had become unresponsive to the same preparation given intramuscularly.
3. No anaphylactic or other sensitivity reactions occurred. (How-

ever, the authors suggest close vigilance during the first half hour of the infusion, until more cases are treated and followed for longer periods).

4. ACTH by this route may overcome functional involution of the adrenal cortex following prolonged cortisone therapy.

The initial dosage currently recommended is 20-25 I.U. dissolved in 500 cc of 5 per cent glucose solution in distilled water given intravenously over an 8-hour period once daily. This dosage is recommended for all age groups except for children under six years of age, for whom about half this dose is advised. When optimal clinical effectiveness has been achieved, the practice has been to repeat the infusion on alternate days for several doses, then every third day, and so on, until the minimal maintenance dose is established. Epinephrine is the drug of choice for sensitivity phenomena. To avoid sudden overdosage, a long hypodermic needle is advisable.

Intravenous therapy with ACTH should be carried out only in the hospital, and if the patient is properly supervised there is apparently little risk. It has been emphasized that because ACTH is rapidly metabolized cummulative effects do not occur.

LONG-ACTING ACTH

Considerable research was necessary to develop a satisfactory vehicle which, by delaying absorption, prolonged the action time of a given dose of ACTH. Lindemann *et. al.* tried two such preparations of ACTH, one in gelatin, the other in sesame oil, and compared their therapeutic efficacy with that of the standard lyophilized ACTH. The observations revealed that the gelatin suspension of ACTH appeared to be superior to intermittent doses of lyophilized ACTH at the same dosage level, and greatly superior to ACTH in sesame oil. These investigators were unable to explain the lack of efficacy of ACTH in sesame oil. They concluded that "a suitably prepared, long-acting percutaneous preparation provides greater and more sustained adreno-cortical stimulation than does intermittently administered, lyophilized ACTH".

Research at the Armour Laboratories, together with aforementioned observations and clinical trials by others, led to the recent introduction of "ACTHAR-Gel", which consists of ACTH in fluid gelatin and is characterized as an "extremely low solids preparation." It is superior to the previous "ACTHAR-Gel" which contained a mixture of gelatin and propylene glycol.

The rule is not absolute that long-acting ACTH is given once every 24 hours. Indeed, as the clinical remission is achieved, it is sometimes adequate to repeat the injection only once in 48 or 72 hours. Thus, a minimal maintenance dose is established by diminishing both the dosage and frequency of injections. Conversely, the larger dosage requirements should be given in more frequent injections, but not oftener than once every 12 hours.

Clinical observations to date suggest that cumulative effects of long-acting ACTH are curiously rare. The introduction of these preparations is still too recent and published literature currently too sparse for final conclusions, but the future appears promising in the light of evidence at hand, since the infrequent injections necessary with long-acting ACTH renders this hormone more competitive with parenteral cortisone, which need be given only once in 24 to 48 hours.

A similar preparation has been introduced by Wilson Laboratories un-

der the name of "Purified Corticotropin-Gel". It is of practical interest that, since the average patient is maintained on about 40 U.S.P. units every 24 hours, the actual drug cost to the patient is less than $1.50 per day.

Reasonably intelligent patients can be taught self-administration, using the preferred subcutaneous route. Three concentrations are available, namely, 20, 40, and 80 units per cc., respectively. Accordingly, U20, U40, and U80 insulin syringes may be used to simplify dosage measurement. (ACTHAR-Gel is available in concentrations of 20 and 40 units per cc., while the Wilson preparation is available in concentrations of 40 and 80 units per cc.) Brief massage should follow the injection. Obviously, long-acting ACTH should NEVER be given intravenously.

NEWER CONCEPTS OF MODE OF ACTION OF ACTH AND CORTISONE

The basic hypothesis of the response of the "anterior pituitary-adrenal cortex axis" during stress is that the respective hormones of these structures exert their effects primarily at the cellular level. The anterior pituitary responds to demands of the organism for adrenal cortical hormones, releasing ACTH during stress in amounts necessary to effect increased secretion and hyperplasia of the adrenal cortex. Conversely, when an excess of cortical hormone is introduced the anterior pituitary inhibits ACTH secretion which may result in compensatory atrophy of the adrenal cortices (Ingle). In addition to the inhibitory action of cortical hormones it is postulated that the hypothalamus and epinephrine possess monitoring and stimulating influences, respectively, over the release of ACTH. Selye has observed deleterious influences as a result of "hypercorticalism" under certain experimental conditions such as high-protein, high-sodium diets and unilateral nephrectomy, thus theorizing that adrenal cortical hormones are intimately associated with the etiology of the group of diseases termed "adaptation diseases." As Ingle points out, if this concept is true, "it will represent the greatest advance in the understanding of disease since the introduction of the germ theory." It remains to be proved.

It is generally agreed that cortisone and compound F are possessed of highly specific anti-inflammatory and anti-allergic activity, yet there is apparently no specificity in terms of diseases responding to these hormones "since any type of cellular reaction to injury is apparently modified, irrespective of cause" (Forsham). While the action of ACTH and cortisone is basically at the cellular level, and the cell is thus protected against effects of injurious agents at any stage prior to necrosis (that is, the damage is reversible), the exact *modus operandi* is not understood at this time.

ORAL CORTISONE

It is now well documented that cortisone is essentially as effective orally as parenterally. One may expect that the oral will virtually supplant the parenteral preparation except in cases in which the oral route cannot be utilized. By the oral route a higher concentration occurs in the blood earlier and more effectively than by the intramuscular route, although the duration of action is only about 6 hours. The clinical results and physiologic effects are equally as good by this route. However, the daily requirement is said to be from 1.2 to 1.5 times greater than intramuscular dosage.

There is an important fundamental difference between these two routes

of administration which should be borne in mind when tapering off dosage. By the intramuscular route due to slow absorption, the action of the hormone persists for about seven days after the last injection. This *gradual* fall in concentration affords the adrenal cortices an opportunity for gradual reactivation. After cessation of oral therapy, on the other hand, the exogenous hormone is totally dissipated in *two* or *three* days. In either case, a temporary exacerbation of the disease state being treated is the rule, but this usually persists less than *five* days. If it persists longer, failure of therapy is suggested.

"INTRA-ARTICULAR" CORTISONE

Kendall's compound F (Reichstein's "substance M") is now termed "hydrocortisone." This hormone is distinct from cortisone although both hormones are synthesized from a bile acid. It has been recently made commercially available as "Hydrocortone" (Merck) which is intended for *intra-articular injection only* in select cases of rheumatoid arthritis and osteoarthritis. Injected into the articular cavity of a rheumatic joint, this substance was shown to be much more effective than cortisone in quelling synovial inflammation. Hollander *et al* gave nearly 700 such injections in 129 cases without untoward effects. Prompt amelioration of signs and symptoms, variable in degree and duration, was observed in sixty-nine cases of rheumatoid arthritis. Curiously enough, even more prompt, more complete and more prolonged relief occurred in thirty-nine cases of osteoarthritis. Injections may be repeated with impunity. In all cases the duration of improvement ranges from several days to several weeks.

Situations in which this form of therapy may be of distinct value are:

1. Involvement of only one or two joints in rheumatoid arthritis or osteoarthritis.
2. Active inflammation in only a few peripheral joints in the presence of others which are ankylosed or "burnt out."
3. Cases in which cortisone and ACTH are contraindicated to relieve severe rheumatoid or osteoarthritis.
4. As a supplement to ACTH or cortisone when too large doses of either are required to suppress severe pain in a few joints.

The dosage ranges from 10 to 50 mg. depending on size of the joint and response to the hormone.

Hydrocortisone is contraindicated in any of the specific infectious arthritides, such as tuberculous or gonococcal arthritis.

DOSAGE OF ACTH AND CORTISONE

Improvement in clinical signs and symptoms and the avoidance of undesirable "side effects" are still the basic criteria of dosage. In a given case with normally functioning adrenal cortices, it is said that about two and one-half times as much cortisone as ACTH is required for the desired therapeutic end-point (Hench *et al*). Twenty-four hour dosage ranges from 40 to 160 I.U. for ACTH and from 100 to 400 mg. for cortisone. *The basic principle of gradually tapering off dosage of either drug remains inviolate!* Laboratory tests suggested as an adjunctive (but less reliable) guide to dosage include leukocyte count, percentage of lymphocytes, eosinophile count, total protein, blood sugar estimation, the electrocardiogram, and serum chloride determination.

Subacromial Bursitis and Tenonitis

These painful conditions of the shoulder need adequate treatment and care to avoid pain and disability

K. ARMAND FISCHER, M.D., *Department of Surgery, University of Louisville, Louisville, Kentucky*

Subacromial bursitis is a painful inflammatory process in the bursa, usually secondary to a calcium deposit in the musculotendinous cuff of the shoulder or, occasionally, to injury. Codman attributed the calcium deposits to multiple trauma and "wear and tear" on the musculotendinous cuff of the shoulder.

INCIDENCE AND SYMPTOMS

Acute subacromial bursitis occurs mostly in the middle-aged group, predominantly among women. The patient will frequently give a history of performing some unaccustomed work with the shoulder or taking part in physical exercise which has not been practiced for a while.

Early symptoms begin with pain in the region of the deltoid attachment to the humerus. Even at this stage, pain can be produced by pressure over the tuberosity of the humerus. A little later, pain and discomfort involve the shoulder region and some swelling occurs. At times, redness and excessive swelling occur when extremely large calcium deposits are present. The more extensive reactions usually require administration of narcotics for relief of pain.

Roentgenographic examination may reveal calcium deposits in the region of the shoulder, ranging from pin head in size to large, soft, calcific masses. When calcium cannot be seen, the deposits in the musculotendinous cuff have probably ruptured and have been absorbed. In some cases, bursal symptoms develop slowly and pain, although minimal, will have been present for weeks. Gradually, the shoulder becomes stiff and painful. Frequently, calcium deposits cannot be detected roentgenographically.

In cases of acute subacromial bursitis in which treatment is not instituted, the violent inflammatory process will gradually subside in from seven to ten days. Other symptoms often will then appear, such as pain in the trapezius, loss of shoulder motion, and pains down the in-

ner side of the arm and the forearm. As the process becomes subacute, chronic extreme muscular atrophy occurs over the shoulder area and stiffness in the shoulder is marked. At this stage, roentgenograms of the shoulder region frequently reveal bone atrophy and osteoporosis.

TREATMENT

In the majority of cases of acute bursitis, conservative care suffices. Sedatives are used for rest, and, when necessary, opiates are administered for relief of pain. As soon as possible, the patient should be instructed in ways to keep the arm away from the chest and thus prevent the adducted painful shoulder. When the patient is resting in bed, the arm should be abducted on pillows. When sitting in a chair, the arm should rest away from the side on a table or bed as near a 90 degree position as possible. This position frequently relieves the pain.

Hot applications are most beneficial for the average patient. Warm, moist heat should be applied continuously day and night in acute cases. As the acute condition subsides, dry infra-red heat may be substituted.

Exercise—All patients should be taught pendulum exercises early, followed by circumduction exercises, as well as trying to abduct and externally rotate the arm and place the hand behind the head, as well as how to rotate the arm internally and place the hands behind the back while standing. The exercises should be carried out conscientiously every hour by the clock.

Other forms of treatment — Injections of novocaine are occasionally permissible in mild acute cases for relief of pain and for instructions in exercises with preliminary stretching of the shoulder. Needling of the calcium deposit or washing out the bursa with saline solution are methods which have their advocates but they are painful procedures and require hospitalization. Cold applications should be applied afterwards, followed by exercise. After 24 hours, hot packs are used and exercise again is carried out.

Roentgen therapy is of some value in mild and moderately acute cases. All patients thus treated should have exercises afterward with instructions to keep the arm abducted. Usually the acute symptoms subside in from five to seven days. The patient should be instructed in the use of infra-red heat every 2 or 3 hours and continuation of exercises until complete motion is obtained.

Operation is indicated in some cases. If large or moderate-sized calcium deposits are present associated with severe acute symptoms, surgical evacuation of the tendon and bursal contents is the best method for relief of pain. After 24 hours, exercises are begun to prevent stiffness and are continued until motion is free.

Occasionally, patients are encountered who have calcium deposits that have been present for several years. Pain will be acute, then subside only to become painful again in several months. Surgical excision affords the best means for relief.

Treatment is more difficult in subacute and chronic bursitis. Due to long usage of sedatives and narcotics for relief of pain, addiction is common. Intelligent and understanding care must be employed by the physician, and a daily physical therapy routine of stretching, heat and exercise must be carried out for several months.

Occasionally, subacromial bursitis is present in both shoulders, but usually only one shoulder is affected. If both shoulders are involved, pain

(Continued on page 458)

A Diagnostic Aid for Migraine

Recognition of the horseshoe symbol, if corroborated, will aid in diagnosis of migraine

THEODORE S. HEINEKEN, M.D., F.A.C.P., *Bloomfield, New Jersey*

Migraine is one of the most common conditions encountered in medical practice. The problem of headache is complicated in that signs and symptoms for the many types of vascular headaches are so varied that diagnosis is most difficult. Migraine in itself has many associated symptoms. Often the patient will stress the accompanying gastro-intestinal symptoms rather than the severity of the unilateral headache from which he suffers. The chief gastro-intestinal complaints appear to be nausea, vomiting, vertigo, severe fatigue, and abdominal distress.

In my effort to simplify the problem of diagnosing migraine, I have tried to observe a sign common to most of these patients. Within a three-year period, I was able to observe one which might be established as typical. It is located on the forehead and was observed in 88 per cent of the migraine cases I examined. I feel that this sign is so common that, if corroborated, it will eventually aid physicians in making a diagnosis.

THE HORSESHOE SYMBOL

The sign which was found to occur commonly in migraine patients can be described as follows:

A flat space or concave pouch, resembling a horseshoe, is observed between the eyebrows, just above the base of the nose, after the patient wrinkles up his forehead and raises his eyebrows as high as possible. This area, comparatively free from creases, is slightly wider at the top than at the bottom, thus forming the horseshoe shape. The tip of the little finger will fit into this space in many cases. In others it may be a flat area.

I routinely look for this sign in all cases in which gastro-intestinal complaints are present in addition to a history of unilateral headache. If the history obtained is that of typical migraine, and if the patient's headaches can be relieved by administration of ergotamine tartrate and caffeine (Cafergot), ergotamine tartrate (Gynergen), or dihydroergotamine

(D.H.E. 45), and/or if the sign is present, a postive diagnosis of migraine is assured.

Figure 1. The migraine sign can be seen between the eybrows, above the base of the nose.

RESULTS

Of the patients I examined and who had gastro-intestinal complaints and who were proved to have migraine, only 12 per cent did not have the sign.

Of the patients who had gastro-intestinal complaints and who were not proved to be migraine sufferers, 16 per cent had the sign.

It can be concluded that the sign is reliable in about 88 per cent of patients who suffer from migraine and who complain of gastro-intestinal symptoms.

REPORT OF A CASE

The following case history is typical: A man 48 years old stated that he had had unilateral headaches since adolescence, usually accompanied by naseau and vomiting. The patient had observed that ingestion of certain foods caused the headaches, and he therefore had learned to avoid chocolate and creamed and fried foods. He had taken laxatives for many years to relieve constipation, since he noticed that the headaches were more severe when he was constipated.

This patient was first seen in 1949 at which time the Migraine Sign was found on physical examination (fig. 1). There also was some tenderness noted in the abdomen to the right of the umbilicus. A rectal fissure was also present. Blood count, sedimentation rate and gastric analysis were all found to be within normal limits. Roentgenographic examination of the gastro-intestinal tract revealed the presence of a duodenal ulcer. Roentgenograms of the gallbladder and barium enema were both negative. The patient was treated for duodenal ulcer and has showed improvement. He now occasionally has unilateral headaches and some nausea, but little vomiting.

SUMMARY

It is again emphasized that most of my patients come to me originally with gastro-intestinal complaints, some of whom have migraine. The use of the diagnostic horseshoe symbol, or migraine sign, is to simplify the diagnosis of migraine.

ECTOPIC PREGNANCY

The first record on extrauterine pregnancy was credited to Albucasis, an Arabian physician, practicing in Spain about the middle of the 11th century (Bauhin, Gynecorum sive de Mulierum Affectibus Comentarii, 1586). The first successful operation for ectopic (tubal) pregnancy was performed in 1883 by Lawson Tait

The Family Physician and the Psychiatric Patient

Simple procedures performed by the family physician are of value in relief, or diagnosis, of many psychiatric symptoms

LEWIS DANZIGER, M.D.,
Milwaukee Sanitarium, Wauwatosa, Wisconsin

In the current clamor about the prevalence of psychiatric patients and the scarcity of persons trained to deal with their diagnostic and therapeutic problems, not much has been said about the important contributions which can be made by the family physician. In this paper will be mentioned a number of valuable procedures which can be performed by any physician who has an interest in the problems of diagnosis and who has at his disposal some simple equipment.

If these procedures are sometimes forgotten, it may be because the traditional role of the family physician as the guardian of the people's health has been increasingly curtailed since the turn of the century by the development of medical specialties. General practitioners who might previously have approached situational and emotional problems with confidence, skill and tact have been taught that such matters are the private preserve of a small group.

No one doubts that many types of necessary and valuable treatment can be given most safely, efficiently and economically by psychiatrists engaged in office or hospital practice. These treatments in some cases may be life saving, not only by the prevention of suicide or homicide, but also, for example, by the relief of the hyperpyrexia of Bell's mania or the prevention of collapse and death in delirium tremens. The significant contribution of psychiatry is not at all belittled by mentioning certain procedures which can be performed by the family physician for the study, and often the relief, of certain symptoms commonly associated with mental disorder.

In many cases, certain of these studies and therapeutic procedures will have to be carried out by the family physician because a psychiatrist is not available or because the patient needs immediate attention while waiting consultation with the psychiatrist. The studies, if pursued systematically, will relieve the

psychiatrist of some uncertainties about the diagnosis and will also make it unnecessary for certain patients to see the psychiatrist. All the studies to be mentioned can be made in the office or in a small hospital, without great expenditure of time or money.

HISTORY TAKING

The first study will be the history of the patient and his illness, with special attention to time relationships so that the various events may be listed in the proper order. Certain aspects of the history will be stressed by the physician. Among these may be listed:

1. The occupation of the patient, with close attention for exposure to toxic agents used in the home, farm or factory, such as insecticides,[1] mercury and other metals, solvents and volatile organic compounds.[2]

2. The home situation, with respect to medicines consumed, especially sedatives, headache remedies, sulfonamides, antibiotics, narcotics, thiocyanates, salicylates and "reducing pills." The escape of noxious gases, such as carbon monoxide from the furnace or elsewhere,[3] the temperature of the home, which may suggest further inquiries leading to a tentative diagnosis of hypometabolism,[4] the plumbing, cooking, sleeping and recreational facilties which, if inadequate, may set up intolerable stresses, should also be considered.

3. The personal habits of the patient, especially the consumption of alcolic beverages and of uncooked meats, and excessive craving for salt, sweets and coffee. Knowledge of abnormal food habits and appetites may suggest further studies leading to the diagnosis of impending nutritional failure, trichinosis, adrenal cortex deficiency, hypoglycemia or food allergy.[8]

4. Study of the endocrine glands, with special reference to the gonads, thyroid, adrenal cortex and pancreas. An accurate menstrual history is often of value as revealing presumptive ovarian failure appearing shortly before the psychiatric symptoms.[2] A man's admission that he experiences hot flashes is often significant and this information is rarely volunteered. Many patients recall, but only upon close questioning, that they once had jaundice, or formerly took thyroid extract regularly, or experienced unsually good health during a pregnancy.

These and other items in the history may suggest further inquiries into some possible chemical, endocrine, nutritional or allergic explanation of the symptoms, no matter how obviously psychiatric the symptoms may be.

PHYSICAL EXAMINATION

After the history is taken, the patient is carefully examined in order to detect some serious disease of the endocrine system or liver, early signs of nutritional failure, or the presence of an anatomic lesion in the nervous or vascular system.

Laboratory tests—Simple laboratory tests are often rewarding. Study of the blood may reveal profound and unsuspected anemia. An increase

1. Biskind, M. S., and I. Bieber, Am. J. *Psychotherapy*. 3: 261, 1949.
2. Danziger, L., *Arch. Neurol. and Psychiat.* 51: 462, 1944.
3. Danziger, L., *Dis. Nerv. System*. 6: 365, 1945.
4. Danziger, L., and Josef A. Kindwall. Thyroid therapy in some mental disorders. *Dis. Nerv. System*. 9: 231, 1948.
5. Fischer, R., Georgi, F. Weber, H. and Piaget, R. M. *Schweiz. Med. Wehnscher.* 80: 129, 1950.
6. Foster, T. L., *J. Nerv. and Ment. Dis.* 110: 1, 1949.
8. Rinkel, H. J., Randolph T. G. and Zeller, M.: *Food Allergy*. C. C. Thomas, 1951.
10. Simonelli, G., *J. Cong. Internat. Psychiat.* 2: 7, 1950.

of lymphocytes or eosinophiles may suggest further inquiries about the adrenal cortex or allergies. Tests of liver function[5, 6, 10] and of the thyroid may reveal totally unsuspected deficiencies which often can be corrected rather easily. A glucose tolerance test may reveal the presence of moderate hypoglycemia at the fourth or fifth hour, with significant exacerbation of all the patient's symptoms. Results of the Wassermann test may indicate the necessity for immediate examination of the spinal fluid.

These procedures, even if negative, may be of value in reassuring those patients with somatic preoccupations or anxieties. They will also reassure the family physician and the consulting psychiatrist.

THERAPEUTIC TESTS

Finally, if the previous studies are only suggestive rather than conclusive, therapeutic tests with vitamins, lipotropic factors and hormones should be carried out. If food allergy is present or suspected, the symptoms may sometimes be abolished by having the patient fast completely for four or five days. Anxiety may be strikingly improved by administration of myanesin[9] or even more dramatically by rebreathing or by holding the breath.[7]

These tests and procedures will screen many patients whose peculiar complaints might otherwise be explained only in psychologic terms. They will also reduce to some extent the sad burden of those physicians who complain that 90 per cent of their patients "have nothing wrong with them."

THE PSYCHIATRIC PATIENT

An important contribution can be made to those patients who must be examined by the psychiatrist or who must enter a psychiatric hospital if the situation is explained to them tactfully and without deceit. Many patients who are taken to the consultant or to the hospital under various false pretenses such as "going for a rest in the country," "going to see a neurologist," "going just for an examination," or "just going for a little drive" often remember and bitterly resent these deceptions. Many others who are told tactfully but frankly that they are going to a psychiatrist or a hospital for study and efficient treatment experience a sense of gratitude and relief. In some situations, without doubt, it would not be inexpedient to tell the patient the whole truth, but nearly always it should be possible to avoid saying what is not true.

Needless to say, no consideration of tact or of scientific curiosity or of pride in diagnostic skill should be allowed to interfere with the speedy hospitalization of a patient dangerous to himself or to the community. No more than the briefest study of the patient should be made by the family physician or the psychiatrist outside the psychiatric hospital if there is any danger of homicide or other violence, of dissipation of the family's economic resources or of suicide. In other situations, where no psychiatric emergency exists, the simple studies described may be revealing and may save the patient the inconvenience and expense of hospital treatment.

7. Kerr, W. J., J. W. Dalton and Gliebe, P. A. *Ann. Int. Med.* 11: 961, 1937.
9. Schlau, L. S., and Unna, K. R. *J.A.M.A.* 140: 672, 1949.

Treatment With Methionine of Napkin Dermatitis Caused by Ammoniacal Urine

The use of methionine to reduce ammonia content of urine is of significant value

LOUIS S. GOLDSTEIN, M.D., *Director of Pediatrics, Yonkers Professional Hospital, Yonkers, New York*

The clinical picture of napkin dermatitis or diaper rash is well known and has been frequently described in medical literature. The diagnosis is simple, the odor of ammonia always being present in a greater or lesser degree, depending on the concentration in the urine. The lesions consist of inflamed areas in the region in contact with the diaper, such as the inner thighs, genitalia, buttocks, and lower abdomen, and are usually characterized by blebs and vesicles. If permitted to go untreated, the lesions may develop into severe ulcerations, which are particularly troublesome when located in the external urinary meatus. Lesions may also develop on the infant's calves and heels.

In many cases the disorder is also characterized by frequent cyclical recurrences and the excretion of a highly-colored urine which stains the diaper.

ETIOLOGY OF AMMONIACAL URINE

Until recently it has been accepted without question that ammoniacal urine is produced after excretion by decomposition in the soiled diaper. It has been stated categorically that ammoniacal diaper rash is caused not by the passage of ammonia in the urine but by the ammonia that is formed in the diaper. Yet the endogenous nature of ammoniacal urine is frequently evidenced by a strong odor of ammonia at the very time when the child is voiding.

An increase of ammonia in the urine is an indication of a metabolic upset of the nature of acidosis. I have observed it often in cases of excessive feeding of fat and acid-forming foods in general, in the course of respiratory and other infections, in gastro-intestinal upsets, and in cases of allergy. It has been observed that ammoniacal urine occurs more frequently among artificially fed infants. Other common causes of endogenous ammoniacal urine include trauma, burns, surgical operations, inoculations, and the anamnestic reaction (an increase

or reappearance of immune bodies already present in the system following injection of a nonspecific antigen). The formation of ammonia is a defensive mechanism of the body formed as a protection against acidosis and to replenish the alkaline reserve.

Rapid destruction of body proteins is one of the important causes of acid shift and compensatory increased elimination of ammonia. This in itself would seem to be an indication for replacement with one or more of the essential amino acids.

Feinblatt and Eggerth[1] stated the following: "Normally most of the ammonia resulting from metabolic processes is transformed into urea. When acid bodies are produced in excess, however, the ammonia unites with them, thus furnishing an important means of protecting the pH of the blood." Ammonia is synthesized by the kidneys to conserve the body's alkaline reserve.

RATIONALE OF METHIONINE

I have found that feeding with methionine, an indispensable amino acid, is of outstanding value in the treatment of napkin dermatitis. Methionine corrects ammoniacal urine by restoring the negative nitrogen balance. This usually requires about three days. Its *modus operandi* can best be explained on the basis of physiologic chemistry.

Methionine is a sulfur-containing amino acid having multiple functions in the organism, including growth, maintenance, sulfur metabolism, detoxication, limiting factor, transmethylation reactions, and so forth.

Stress of almost any variety produces an accelerated urinary nitrogen excretion and negative nitrogen balance. Reserve proteins are then broken down and much needed specific amino acids are monopolized for essential nitrogen metabolism. Since the remaining amino acids, not utilized for energy, do not fulfill the requirements for protein synthesis, they are carried to the liver, deaminated and excreted as urea.

Negative nitrogen balance is equal to starvation. In starvation, carbohydrate and fat stores as well as sufficient protein are mobilized to maintain caloric balance and essential protein metabolism. Superfluous (incomplete) mixtures of amino acids not utilized for energy are excreted.

Supplementary methionine arrests the raiding of dispensable protein stores which depresses the excretion of those amino acids which cannot fulfill all the requirements for protein synthesis. The increased nitrogen retention then eliminates starvation and subsequent acidosis.

With the restoration of nitrogen balance by administration of methionine, the ammonia content of the urine is reduced to normal and the cause of the diaper rash is removed.

SAFETY OF METHIONINE

Since methionine is a food, being one of the indispensable amino acids which may be obtained from casein or egg white in considerable proportion, it can be tolerated by children and adults in large amounts.

In *New and Nonofficial Remedies*, 1952, the following appears; "Because methionine is low in toxicity, its use is not likely to be attended by any untoward effects."[2] As a supplement to a high protein diet, an adult dosage of from 3 to 6 Gm. daily is recommended by the Council on Pharmacy and Chemistry of the American Medical Association. In severe cases of liver damage, doses of from 10 to 20 Gm. daily have been used.

1. Feinblatt, H. M. and Eggerth, A. H., *Clinical Laboratory Medicine*, New York, Wm. Wood & Co., 1925, p. 130.

2. *New and Nonofficial Remedies*, American Medical Association, 1952.

The Council also stated that "methionine administered to the mother during pregnancy when an erythroblastic infant is expected and to such infants for 12 days after birth, may be useful to prevent or diminish fetal liver damage found in this disease."

The safety of methionine, even for newborn infants, has been established by the clinical studies of Philpott, Hendelman and Primrose[3]. According to these authors: "All babies who have hemolytic disease receive 0.5 Gm. of methionine daily for at least the first twelve days of life. This is given in doses of .125 Gm. in 5 per cent glucose saline or in the milk. Practically all the babies have taken this mixture with avidity, almost denoting that they required it in their systems."

In my own series of more than 500 cases of napkin dermatitis treated with methionine, untoward effects were conspicuously absent. One infant refused the formula to which methionine was added, because of the taste; a second vomited the formula; and a third developed a generalized macular dermatitis indicative of a sensitization reaction.

In view of the comparative newness of methionine therapy, especially for infants, I watched all babies closely for the possibility of toxic or serious side effects. There were none. Consequently, I regard the use of methionine for napkin dermatitis as a safe method of treatment for general application.

Prophylactic doses of 0.2 Gm. of dl-methionine daily were given to fifty infants continuously from the age of two months until that of six months.[4] At no time did these infants show ammoniacal urine or napkin dermatitis, and there were no ill effects in any case.

TREATMENT

Methionine is easily administered, has an acceptable taste and odor, and produces relatively no gaseous or intestinal discomfort. A satisfactory response is obtained with few exceptions when methionine is employed, using a dosage of 0.2 Gm. daily, given in the infant's daily formula or in tomato juice.

CASE STUDIES

In the past three years methionine has been employed in the treatment of more than 500 infants exhibiting ammoniacal urine. Metiogran* (10 per cent dl-methionine granulated with lactose) was used in all cases.

One teaspoonful of Metiogran contains 0.2 Gm. of methionine, which represents the daily dose for an infant less than one year of age. For infants from one to two years old, 1½ to 2 teaspoonfuls of Metiogran, containing 0.3 to 0.4 Gm. of methionine, are required daily. This preparation is soluble, palatable and stable under adverse weather conditions. It mixes readily in the daily milk formula or tomato juice.

Of the more than 500 cases treated with Metiogran, treatment was successful in all but three. The ammonia consistently disappeared from the urine in from three to four days, napkin dermatitis and ulcerations, including those of the external urinary meatus, cleared up in from seven to ten days. Therapy was continued for at least one week. With the appearance of cyclic recurrences, Metiogran was prescribed for another week or two. Application of zinc ointment was the only local therapy employed.

3. Philpott, N. W., Hendelman, M. and Primrose, T., *Am J. Obst. & Gynec.* 57: 125, 1949.
4. Goldstein, L. S., *Arch. Pediat.* 66: 535, 1949.

*The dl-methionine, granulated, used was Metiogran, a product of The Lobica-Debruille Chemical Corporation, New York, N.Y.

SUMMARY AND CONCLUSIONS

Many cases of napkin dermatitis are endogenous, due to a negative nitrogen balance. In such cases the urine has a high ammonia content when voided. The diaper rash results directly from this irritation, not ammoniacal decomposition after urination.

Methionine, by arresting the raid on the body's reserve proteins, quickly restores nitrogen equilibrium. When this occurs, the ammonia content of the urine returns to normal and napkin dermatitis disappears without local treatment.

In infants the nitrogen balance is easily upset by comparatively minor causes, including colds, bronchitis, tonsillitis, gastro-intestinal upsets, allergy, trauma, burns, inoculations and booster injections, and anamnestic reactions.

Clinical studies show that methionine has little, if any, toxicity, and may be administered safely to newborn and young infants continuously for as long as four months. No untoward effects have been observed.

In a series of 500 cases of napkin dermatitis treated internally with dl-methionine, the therapy was successful in all but three. The ammonia disappeared consistently from the urine in three to four days. Napkin dermatitis and ulcerations, including those of the external urinary meatus, cleared up in from seven to ten days.

BURSITIS

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usually affects only one shoulder at a time.

Persistent shoulder pain is not always due to bursitis. Cervical discs, arthritis, cardiac conditions and tumors of the superior lobe of the lung are often mistaken as bursitis, especially when an old calcium deposit is present in a supraspinatus tendon.

SUMMARY

Subacromial bursitis and tenonitis are of such a nature that inadequate treatment and after care often will result in a painful, disabled shoulder and arm. Conservative therapy with moist packs and sedatives suffices in most acute cases, while operation is of benefit in others. Often, extensive and intelligent physical therapy is necessary in subacute and chronic cases.

NOTES on MEDICAL STATISTICS

POLIOMYELITIS

Author reports on a survey on poliomyelitis cases in the United States in 1950. There were 583 respirator patients of which 60% were from 1950 while 40% had been in respirators one year or more. Two thirds of the hospitalized patients (in 135 hospitals) were over 15 years of age, one half over 20, one third over 25. Up to 10 years of age there were twice as many males as females and over 20 years of age there were 15% more females than males. 80% of the population over 15 years of age possesses antibodies to one or more of the three known types of poliovirus. The peak incidence is now in the 5 to 9 year age group; 25% of the cases are now over 25 years of age. (H. S. Landauer, Dir. of Med. Serv., Nat'l Foundation for Infant. Paral., The Journal Lancet, 9:360, September 1951).

Gamma Globulin in General Medical Practice

An effective prophylactic agent in certain epidemic diseases, gamma globulin studies may aid in further aspects of immunity research

JEREMIAH A. BARONDESS, M.D.
Communicable Disease Center, Public Health Service, Atlanta, Georgia, and The Children's Hospital of Philadelphia, Pennsylvania

INTRODUCTION

The recent evolution of technics which permit the separation of several of the plasma proteins in relatively pure states has provided the physician with a material which shows promise of becoming increasingly important in the handling of many problems in the field of infectious diseases. This material, gamma globulin, separated by the procedures of Cohn and his coworkers[1] is a rich source of antibodies. These substances are concentrated some twenty-five times by the chemical manipulations required for their separation from other components of plasma.[2]

Due to the large size of the plasma pools from which gamma globulin is produced, antibody titers in various lots have been shown to be remarkably constant;[2, 3] These titers may be conceived of as depending primarily upon the presence of endemic or recent epidemic disease in the area from which the blood is drawn; the number and duration of antibodies resulting from particular infections; and the number of donors contributing to the pool.[3] The antibodies contained in gamma globulin appear to reflect the continuing presence of neutralizing antibodies in the extra-cellular fluids following exposure to a variety of infectious agents, with either frank clinical illness or inapparent (subclinical) infections.

Probably about 60 per cent of plasma antibody activity is recovered in the gamma globulin fraction,[4] and the antibody titers in this fraction are stable for long periods at refrigerator or room temperatures.[2]

There are a variety of diseases in which gamma globulin has been used clinically and epidemiologically as a source of concentrated antibodies.

1. Cohn, E. J., *Ann. Int. Med.* 26: 341, 1947.
2. Enders, J. F., *J. Clin. Investigation* 23: 510. 1944.
3. Stkes, J. Jr., *Ann. Int. Med.* 26: 353, 1947.
4. Janeway, C. A., Bull. *New York Acad. Med.*, 21: 202, 1945.

MEASLES

Gamma globulin has been described as the most satisfactory substance available at present for the prevention and attenuation of measles.[3, 4] Ordman, Jennings and Janeway studied a group of presumed susceptibles with exposure within the family. In the group receiving gamma globulin, 71 per cent were protected against measles; 27 per cent had modified measles; and there were 2 per cent failures among sixty-two inoculated children. Of forty-six controls not inoculated, 89 per cent developed measles of average severity; 4 per cent contracted mild measles; and 7 per cent failed to contract measles. These authors gave an intramuscular dose of 0.1 cc. per pound of body weight within five days after exposure for protection against the disease. They recommended about a quarter of this dose if attenuation was desired. They believed that if the material is given more than five days after exposure, somewhat larger doses should be used. The duration of protection is probably at least two weeks, but not as long as from seven to ten weeks.[5]

Stokes, Maris and Gellis[6] also noted striking protection or attenuation in a study of a similar group. 1. Treatment of early measles by these authors, using large doses of gamma globulin (5 to 3 cc.) showed modification of the disease in 77 per cent of those who received it before the rash appeared, and in 43 per cent of those given the drug after the rash had appeared.

Janeway[4] has pointed out that in cases in which modified measles has developed after gamma globulin injection, post-measles complications are only about one-tenth as frequent as among unprotected patients. He has found the material useful in controlling measles in pediatric wards, isolating only the primary case and giving exposed susceptibles a protective dose; susceptible new admissions are also injected for about a 3-week period.

On statistical analysis, gamma globulin has been shown to be more effective per unit volume than either convalescent serum or placental extract in measles prophylaxis.[7]

MUMPS

The place of gamma globulin in treatment and prophylaxis of mumps cannot be finally evaluated. Gamma globulin prepared from normal plasma pools does not appear to protect exposed susceptibles when given in doses up to 50 cc.[3] Further Gellis, McGuinness and Peters,[8] studying an epidemic in an army camp, found that gamma globulin from normal plasma pools in doses of 50 cc. failed to reduce significantly the incidence of orchitis when given within 24 hours of the onset of parotitis. Gamma globulin prepared from mumps convalescent serum, however, when given in doses of only 20 cc. to a comparable group, reduced the incidence of orchitis from 27.4 per cent in the uninjected controls to 7.8 per cent in the treated patients.

Thus, the value of gamma globulin in mumps is at present limited by the amount of convalescent serum available for fractionation. Until globulin prepared from such serum is widely available, it should probably be reserved for the treatment of adult males within the first 24 hours of the disease, the objective of treat-

5. Ordman, C. W., Jennings, C. G. Jr., and Janeway, C. A., *J. Clin. Investigation*, 23: 541, 1944.
6. Stokes, J. Jr., Maris, E. P., and Gellis, S. S., *J. Clin. Investigation*, 23: 531, 1944.
7. Janeway, C. A., *J.A.M.A.* 126: 674, 1944.
8. Gellis, S. S., McGuiness, A. C., and Peters, M. *Am. J. M. Sc.* 210: 661, 1945.

ment being to prevent or to attenuate orchitis.

INFECTIOUS HEPATITIS

Since the first demonstration of the effectiveness of gamma globulin in the prevention and attenuation of this disease, by Stokes and Neefe,[9] confirmation of this work has been amply documented[10-12] both in naturally occurring epidemics in open communities and in outbreaks in institutions. Although initially doses of the order of 0.15 cc. per pound of body weight were used, recent studies[12] have shown that as little as 0.01 cc. per pound is effective. Studies have shown that in the first five or six days after injection the material does not protect, but after this period the incidence of infectious hepatitis is very low. This protection has been shown[12] to last as long as nine months when individuals were in an epidemic situation.

Treatment of early, pre-icteric hepatitis with gamma globulin in large doses[13] has not appeared to alter the course of the disease significantly.

SERUM HEPATITIS

Gamma globulin in serum hepatitis has not provided results as clearcut as those obtained in infectious (epidemic) hepatitis. Grossman, Stewart and Stokes,[14] in a study conducted in an army hospital, gave 10 cc. of gamma globulin to alternate battle casualties, repeating the dose one month later in the injected group. Omitting cases occurring within one week after the injections were given, the overall incidence of hepatitis in the injected group was 1.3 per cent while that in the uninoculated control group was 8.9 per cent. In addition, the cases occurring in the injected group were, in general, mild, suggesting that some degree of attenuation had been obtained with gamma globulin.

A second study[15] was carried out in an Army hospital, which differed from the first in that a single dose of 10 cc. was used. No significant difference in attack rates in treated and control groups was seen, although the onset of hepatitis was retarded by an average of eighteen days.

Preliminary studies in human volunteers[16] appear to support the idea that gamma globulin is not as efficacious in protecting against serum hepatitis as against infectious (epidemic) hepatitis.

GERMAN MEASLES

Although studies on prophylaxis against rubella with gamma globulin are not conclusive, there is some preliminary evidence suggesting that protection is afforded. Stokes[17] reported an instance in which a nurse with rubella intimately exposed five presumably susceptible roommates, each of whom received 5 cc. of gamma globulin four days after exposure. No secondary cases developed. He also noted the exposure of a ward of thirteen infants and children, all presumably susceptible, to an infant with rubella. There were no secondary cases after administration of 2 cc. four days after exposure.

9. Stokes, J. Jr., and Neefe, J. R., *J.A.M.A.* 127: 144, 1945.
10. Gellis, S. S., Stokes, J. Jr., Brother, G. M., Hall, W. M., Gilmore, H. R., Beyer, E., and Morrissey, R. A., *J.A.M.A.* 128: 1062, 1945.
11. Havens, W. P., and Paul, J. R., *J.A.M.A.* 129: 270, 1945.
12. Stokes, J. Jr., Farquhar, J. A., Drake, M. E., Capps, R. B., Ward, C. S., and Kitts, A. W., *J.A.M.A.* 147: 714, 1951.
13. Gellis, S. S., Stokes, J. Jr., Forster, H. W., Brothers, G. M., and Hall, W. M., *J.A.M.A.* 128: 1158, 1945.
14. Grossman, E. B., Stewart, S. G., and Stokes, J. Jr., *J.A.M.A.* 129: 991, 1945.
15. Duncan, G. G., Christian, H. A., Stokes, J. Jr., Rexer, W. F., Nicholson, J. T., and Edgar, A., *Am. J. M. Sc.* 213: 53, 1947.
16. Stokes, J. Jr., Drake, M. E., Henle, G., Henle, W., Bashe, W., and Barondess, J. A. (Unpublished data).
17. Stokes, J. Jr., *Rhode Island M. J.* 24: 423, 1946.

In an institutional outbreak,[18] 320 children were intimately exposed. Of these, 151 received gamma globulin in an average dose of 0.1 cc. per 1 pound of body weight; there were 169 unincoculated controls. Fifty-eight children were later dropped from the study for various reasons. Two cases in each group were omitted within three days after injection

No note was made as to the severity of the cases in the treated group. It would appear that when given on the day of exposure in the dose used in this study, gamma globulin affords some protection against rubella. This protection was evidently lost sometime before the nineteenth day.

McLorinan has used gamma globulin prepared from convalescent rubella serum, and feels that it has been effective in prophylaxis in a dose of 4 cc.[19]

POLIOMYELITIS

Gamma globulin has been shown to contain large amounts of neutralizing antibodies against the Lansing, Brunhilde and Leon strains of poliomyelitis virus.[20] These have been found to be present in approximately equal titer. Further, 0.1 cc. given intraperitoneally will protect a mouse against simultaneous intracerebral inoculation of virus. These studies have been confirmed in cotton rats and monkeys.[17] Definitive studies in humans on protection with gamma globulin have not yet been carried out, although there was suggestive evidence from Bloxam's study[21] that the material may protect in humans as well as in animals. Large-scale epidemiologic trial of gamma globulin in poliomyelitis has been planned[22] and the results of such studies must be awaited before the value of the material in the prophylaxis of this disease can be evaluated. Its lack of efficacy in the treatment of poliomyelitis may be indicated by the fact that Bahlke and Perkins found that it had no effect when given to alternate preparalytic cases during an epidemic.[23]

OTHER DISEASES

The results of treatment of scarlet fever with gamma globulin have been reported to compare favorably with those obtained with scarlet fever antitoxin,[24] although no comparison was made with a group in which optimal therapy with antibiotics was carried out. Also, the material has been said to be of use in treatment of the so-called anginose type of infectious mononucleosis.[25] Janeway[7] has reported that in limited trials no protection against varicella was observed with doses ranging from 5 to 20 cc. Cheever and Daikos[26] have demonstrated the presence of neutralizing antibody for herpes simplex in gamma globulin; applicability of this finding to human infections has not yet been demonstrated.

USE OF GAMMA GLOBULIN PREPARATIONS

Current gamma globulin preparations should only be given intramuscularly, since intravenous use may

18. Subcommittee on Gamma Globulin of the Committee on Public Health, Medical Society of the County of New York, New York, Med. Dec. 5, 1949.
19. McLorinan, H., *M. J. Australia.* 2: 390, 1950.
20. Bodian, D., *Proc. Soc. Exper. Biol. and Med.* 72: 259, 1949.
21. Hammon, W. McD. (Unpublished data).
22. Bloxsam, A., *Texas State J. Med.* 45: 468, 1949.
23. Bahlke, A. M., and Perkins, J. E., *J.A.M.A.* 129: 1146, 1945.
24. Silver, F. F., *Am. J. Dis. Child.*, 78: 437, 1949.
25. Bower, A. G., Affeldt, J. E., and West, H., *J. Pediat.* 35: 58, 1949.
26. Cheever, F. S., and Diakos, G., *J. Immunol.* 65: 135, 1950.
27. Stokes, J. Jr. Personal communication to the author.

result in serious reactions.[27] In a summary of 1,843 intramuscular injections, Janeway[7] has emphasized the safety of the material when given by this route. The incidence of reactions was 1.7 per cent. Half of these reactions were local, consisting of soreness or transient swelling, and half were general, chiefly fever, with one anaphylactoid type observed.

The danger of transmission of the virus of serum hepatitis in gamma globulin preparations as currently used in this country appears negligible.[28] Indeed, it seems justifiable to conclude that Cohn's technique for the preparation of the material either inactivities the serum hepatitis virus, eliminates it from the gamma globulin fraction, or neutralizes it.

MECHANISM OF ACTION

Although in the early studies on gamma globulin[10] it was suggested that the material protected against infectious hepatitis by the induction of passive immunity, more recent studies[12] have suggested that a more complex mechanism may be involved. In view of the prolonged protection against infectious hepatitis observed in three institutional outbreaks, Stokes and his co-workers have suggested that after injection of gamma globulin, with induction of passive immunity, active immunity may be superimposed through continuing exposure to the virus, which may occur without the advent of clinical illness. The soundness of this idea will best be evaluated after more studies have been carried out, not only in infectious hepatitis but in the several other diseases in which gamma globulin has been shown to be of use.

28. Stokes, J. Jr., Drake, M. E., Korns, R., and Janeway, C. A. (To be published).

SUMMARY AND CONCLUSIONS

Gamma globulin has been established as an effective prophylactic agent in measles and infectious (epidemic) hepatitis. It is useful, when prepared from convalescent mumps serum, in reducing the incidence of orchitis in mumps. There is reason to believe that it may prove of value in prophylaxis against poliomyelitis, and there is preliminary evidence that it may protect against rubella. Its proper application in serum hepatitis and varicella is yet to be established.

In addition to these findings, and in view of the relative uniformity of antibody titers and protection in several diseases, it seems reasonable to conclude that the donors from whose plasma the material has been prepared have, in general, been immunized against these diseases, either by clinical or subclinical infection, and this reasoning may be extended to the general population from which those donors were drawn. Thus, studies on gamma globulin show promise of aiding in basic research in the host-parasite relationship, including certain aspects of immunity as well as virus ecology.

SIDE GLANCES at MEDICAL HISTORY

OZENA

The clinical entity: atrophic changes in the nasal mucosa; formation of crusts in the nasal passages, accompanied by a uniquely offensive odor, was first established by B. Fraenkel in 1876.

THERAPEUTIC TRENDS

Duration of Action of Different Insulins

The tests were made on sixty-four healthy students at the University Hospital, Leyden. The students were divided into eleven groups, including one control group. All remained resting during the experiment and for 7 hours preceding it, and all received hourly feedings of 10 Gm. of carbohydrate and 30 ml. of water, commencing at 6 a.m. From 7 a.m. on, the blood sugar level was estimated hourly until it had returned to the pre-injection content. At 8 a.m. each group except the control group, received 20 units of one of the ten insulins being studied. The results are assumed to be applicable equally to diabetic patients as far as the duration of the effect of the different insulins is concerned.

The results with the various insulins were as follows: ordinary insulin produced its lowest blood sugar level within 1 hour, with return of the level to normal in 8 hours; protamine-zinc insulin was active for 18 hours, with a mimimum blood sugar level at 5-8 hours; "di-insulin" produced its greatest decrease in the blood sugar level in the first 3 hours, while being active for 16 hours; "iso-insulin" produced a rapid fall in the first hour and was effective for 17 hours; globin insulin proved identical in action with "di-insulin"; two brands of "N.P.H. 50" insulin were effective for 11 hours, with a maximum effect at 4 and 3 hours, respectively.

(Gerritzen, F., *Brit. Me. J.*, 1: 249, 1952).

Use of Terramycin In Urinary Tract Infections

The antibiotic value of terramycin was assessed on the basis of results obtained in 107 patients with chronic urinary tract infections. The drug was administered in the usual oral dose of 0.5 Gm. given at 6-hour intervals. The average dosage for a treatment period of 6.5 days was 16 Gm.

Results. Bacterium coli (forty-six instances) and Aerobacter aerogenes (seventy-one instances) were cleared during or soon after a course of treatment. Strains of Proteius vulgaris (twenty instances) and staphyllococci (seven instances) persisted in a greater proportion of cases and appeared even more frequently for the first time during or after terramycin treatment. Strains of Pseudomonas aeruginosa (eight instances) and of enterococci (five instances) were usually eliminated, but new strains frequently appeared.

Sterile urine was achieved in six patients only; in eleven others, new organisms appeared, although one or more types had been cleared from the urine. In thirteen instances of mixed infection, the original organisms persisted, with additional new ones appearing in five cases after commencement of the therapy.

Of the pure or predominant strains isolated, 102 were obtained before and thirty-two after treatment. Of the latter, thirty needed not less than 400 mg. of terramycin per ml. before being cleared.

In summary, good clinical results were obtained in about 50 per cent of the patients; in 29 per cent the results were equivocal; and in 22 per cent no clinical or bacteriologic improvement was experienced. Indeed, in many of the latter group of patients the infections worsened, and most of the fourteen deaths which occurred fell in this group.

The most serious feature of the treatment was the frequency with which staphylococci appeared, multiplied and aggravated the condition. Resistant staphylococci are now a major hazard in the application of antibiotics, and a new approach to their control is an urgent need.

(Womack, C. R., *et. al.*, *Arch Int. Med.* 89: 240, 1952).

Khellin in the Treatment of Angina Pectoris

This clinical and experimental evaluation of khellin is based on the extended study of fourteen patients with angina of effort. The average dose of khellin given by mouth was 150 mg. Some patients proved intolerant to as little as 50 mg. of the drug, and others were able to absorb daily doses of 300 mg. without experiencing side reactions. Distinct reduction in anginal attacks was obtained, however, in only seven of the patients, all of whom suffered some toxic effects.

Tolerance was increased when the drug was administered by the intramuscular or intravenous routes, but the injections proved painful. Parenteral administration of single doses or daily maintenance doses of khellin failed, moreover, to demonstrate an increase in the patients' tolerance to standard exercise or any changes in the electrocardiogram. Glyceryl trainitrate (0.43 mg.), on the other hand, produced significant increases in exercise capacity when given under similar conditions.

Khellin also failed to effect any significant changes in cardiac output or in pulmonary arterial or brachial pressure, although there appeared to be a very slight rise in systolic and diastrolic pressure in all instances. It is therefore concluded that khellin seems of doubtful value in the treatment of angina pectoris, although its effect at higher dosage levels remains to be probed. Such an investigation is impracticable at present, because of toxicity limitations.

(Robertson, H. S., Hultgren, H. N., and Stevens, L. E., *J.A.M.A.*, 148: 465, 1952.)

Influence of Probenecid on Serum Penicillin Concentration

Seventeen adult convalescent patients not suffering with renal, gastrointestinal or cardiovascular disorders were treated with single, oral daily doses of 500,000 units of penicillin first without and then with the addition of variable doses of "Probenecid." This drug is a benzoic acid derivative (p-(di-n-propylsulfamyl)) which produces the same effect as "carinamide" but is effective in smaller doses (Cf., Bever, *et al.*, *Proc. Soc. Exper. Biol. & Med.*, 74: 772, 1950); it also has been found to be of rather low toxicity. The therapeutic value of the drug consists in the fact that it depresses the renal tubular excretion of penicillin.

Experiments with oral doses of 500,000 units and with 1,000,000 units of penicillin administered alone and then with the addition of 1 Gm. of probenecid showed that the drug effected a penicillin serum level double that produced by this antibiotic alone in each instance. It was also observed that a dose of 500,000 units of

penicillin plus 1 Gm. of protenecid resulted in a serum concentration which was greater than that produced by 1,000,000 units of penicillin alone.

It is therefore concluded that oral penicillin plus probenecid may largely replace the other now currently applied methods of administering this antibiotic. In the authors' experience, an oral dose of 500,000 units of penicillin plus 1.0 Gm. of probenecid given every 12 hours will suffice for the majority of penicillin-sensitive organisms. It should also be noted that none of the patients treated by the authors experienced toxic manifestations either during or subsequent to probenecid admintration.

(Frisk, A. R., Diding, N., and Wallmark, G., *Scand. J. Clin. & Lab. Invest.* (2): 83, 1952.)

Conservative Management of Acute Urinary Suppression

The claim is made that acute urinary suppression can be managed successfully by conservative measures which are simple in approach and technique. The claim is supported by the author's treatment, in this manner, of thirty-seven consecutive patients with severe urinary supression. Each of these patients had a urinary output of less than 100 cc. per day for three or more consecutive days.

The conservative steps specifically directed to the correction of the urinary suppression were concerned with the restoration of the fluid and electrolyte balance by recourse to cation exchange resins, and of minimum caloric requirements by the administration of carbohydrates. The results obtained by the author and his judicious application of these measures approximated a survival rate of 80 per cent.

(Stock, R. J., *Bull. N. Y. Acad. Med.*, 28: 507, 1952.)

The Cholesterol Content of Foods

Few systematic studies have as yet been carried out on the cholesterol content of foods, the notable exception being milk and eggs. In the present report the author gives the results he obtained in investigating the cholesterol content of the four following groups of animal foods: 1. Dairy products and eggs—2. Meat and edible fats—3. Fish and fish products—4. Marine animal oils.

His data show that the richest sources of cholesterol are: brain, egg yolk, cod liver, cod roe and marine animal oils; other rich sources are butter margarine, whale and herring oil, and glandular organs such as liver, lungs, kidney and thymus. The various types of cheese examined contained from 33 to 157 mg. of cholesterol per Gm.

Lean meat was found to contain approximately from 60 to 85 mg. of cholesterol per 100 Gm., with only minor differences for the various kinds of meat. Fish and fish products rated about 60 mg. of cholesterol per 100 Gm., and herring and mackerel registered distinctly higher in this respect.

It was found, in other words, that lean meat, fish and fish products constitute important cholestrol sources, a fact which is insufficiently appreciated, and that relatively too much emphasis is placed on milk and animal fat as suppliers of cholesterol. Animal fat was shown to contain only moderately higher amounts of cholesterol than lean meat.

It is therefore concluded that a high fat diet is not synonymous with a high cholesterol diet and that, conversely, a low-fat diet is not necessarily a low-cholesterol diet. If a really low-cholesterol diet is desired, animal products must practically be excluded.

(Pihl, A., *Scand. J. Clin. & Lab. Invest.* 4 (2): 115, 1952.)

Bleeding from the Rectum

Bleeding from the anal orifice demands investigation. The rectum is the terminus of the gastro-intestinal tract and blood which issues therefrom may come from any place between mouth and perineum. In general, bright red blood has its origin in the colon or rectum, and the dark blood of tarry stools (melena) indicates that this blood has passed through the small intestine. However, there are also instances in which blood may pass through the small and large intestine and reach the rectum while still bright red. This may occur with massive hemorrhage from esophageal varices, from hiatus hernia, gastric neoplasm or peptic ulcer, when increased peristalsis hurries the blood to the rectum. Fortunately, the vomiting which takes place in most cases of massive gastric hemorrhage will suggest its localization.

Blood which has been altered by its passage through the small intestine may appear mixed with stool and be passed in the form of sticky, foul-smelling and tarry excreta (melena). If such blood has gone through the upper tract more quickly then chyme, it may not have changed color completely and will appear dark red. Such a stool gives a 4-plus benzidine or guaiac reaction. Iron compounds prescribed for anemia also produce black tarry stools, while ingestion of beets results in a dark red stool which may be mistaken for blood.

Colonic and rectal bleeding is always mixed with stool unless the blood issues suddenly and profusely. Cancer of the rectum and ulcerative colitis, for example, produce blood churned with stool. On the other hand, large papillary lesions of the cecum or ascending colon may bleed constantly but not sufficiently to be detected by the patient. Sudden, massive colonic hemorrhage is usually of benign origin. Blood-mixed stools are often produced by benign and malignant lesions as low as the rectosigmoid. Bleeding from the hemorrhoidal or anal area can usually be differentiated by its association with the passage of stool and the origin of the blood, that is, whether it came from the inside or the outside of the sphincters. Anal papilla and fissures when traumatized by the passage of stool will cause deposition of small amounts of blood at the anal margin. Chronic recurrent fissures or anal scars that are epithelialized and inactive are often the seat of minute telangiectases that bleed on passage of hard stool. The commonest source of blood which soils the undergarments are permanently prolapsed hemorrhoids, or rectal mucosa and prolapsed ulcerated anal papillae. A prolapsed polyp may also occasionally be involved. Among the more obscure causes of bleeding may be listed: ruptured telangiectases, submucodal infarcts, the per rhexin hemorrhage of hypertensives, the bleeding from diverticulosis and hemorrhagic diatheses.

Patients with melena due to a pathologic lesion require a complete upper gastro-intestinal examination. Red blood from the rectum, on the other hand, should first be traced,

if possible, to its local origin in the colon or rectum. Anoscopic and proctosigmoidoscopic examination followed by colon roentgenograms made with double air contrast technic are indicated when the blood is mixed with stool. Anorectal bleeding, that is, bleeding after passage of stool or "on stool," may be diagnosed adequately by anoscopic and proctosigmoidoscopic examination, providing the cause of the bleeding is known. Finally, in case of changed bowel habits, no matter how slight, roentgenographing of the colon is always necessary because of the danger of carcinoma. Multiple exploratory technics will be necessary.

(Turnbull, R. B., *Cleveland Clin. Quart.* 19: 62, 1952.)

Evolution of Eosinophil Counts

By making use of Randolph's staining method, the authors studied the normal diurnal variations in the eosinophil count in healthy and arthritic individuals in response to stress. The effect of meals was found to be negligible. All individuals showed a high early-morning level in the eosinophil count. The level fell spontaneously by as much as 40 per cent in the afternoon.

Day-to-day eosinophil counts must, therefore, be made at the same time of day, and an eosinopenia apparently induced by corticotropin or other agents cannot necessarily be attributed to the agent unless the latter was given in the afternoon and produced a fall of over 40 per cent in the count extending over more than two hours. It is thus important to make hourly counts for four hours following injection, because the maximum fall is sometimes experience at the second or third hour.

(J. N. Swanson, W. Bauer and M. Ropes, *Lancet*, 1: 129, 1952.)

Basal Metabolism of Pepsin

Twenty-one duodenal ulcer patients were observed to secrete, on the average, three times as much pepsin as did twenty-nine controls. The secretory behavior observed, on the other hand, in a group of five gastric ulcer patients and in five patients with carcinoma fell in the normal range. A similar increase in acid secretion was observed in duodenal ulcer patients in the basal state. A high degree of correlation was moreover found to exist between the amounts of pepsin and of acid secreted per hour, respectively. It seems, therefore, that the peptic and parietal cells, when in the basal state, probably respond to some common influence which may be of vagal origin.

(H. D. Janowitz and F. Hollander, *J. Clin. Invest.*, 31: 338-340, 1952.)

Relationship of Glandular Mucoprotein from Human Gastric

Isolation from human gastric juice of a "glandular mucoprotein" is described which is claimed to be either Castle's intrinsic factor itself or to be a substance containing this factor.

Clinical justification is based on the result obtained among nine patients with pernicious anemia untreated or in relapse, who had not responded to daily doses of vitamin B_{12} ranging from 7 to 30 ug. but who did respond when the same dose was combined with glandular mucoprotein. More precisely, a definite hematopoietic response was obtained in seven of the nine patients. In three patients it was optimal, parenteral injection of vitamin B_{12} producing no further response, and in two patients it was suboptimal.

(Glass, G. B. J., Boyd, L. J., Rubenstein, M. A., and Svigals, C. S., *Science*, 115: 101, 1952.)

Tetanus

Evaluation of 372 cases, observed in a 20 year period. The majority of injuries leading to tetanus involved agrarian workers. Children are particularly exposed as they walk barefoot. The second decade of life shows the highest incidence rate. Wounds of any part of the body may cause tetanus but the limbs are more frequently involved than the trunk. Puerperal tetanus has been known for a considerable time; its prognosis is grave. It is most frequent after criminal abortion. Tetanus occurs after exposure to cold and then has a poor prognosis. Author observed four such cases and also four cases after burns. The average incubation period was 12.8 days in injuries of the legs, 12.8 days in injuries of the feet, 10.9 days in injuries of the thighs, 8 days in injuries of the trunk, 11.6 days in injuries of hands and fingers, 9.2 days in injuries of the arm, and 6.8 days in injuries of the neck or head. The prognosis of tetanus is more favorable when the incubation period is longer and also when the clinical symptoms develop slowly. Cases with initial pharyngeal and diaphragmatic spasm almost always end fatally. Prodromal symptoms are: headache, vertigo, sweating, fatigue, insomnia, photophobia, pain in the lateral thoracic area; later one finds disturbances of swallowing and exaggerations of tension reflexes. (W. Koele. Langenbeck's Arch. f. klin. Chir. u. Deutsche (W. Koele. Langenbeck's Arch. *Deutsche Ztschr.*, 269: 37, 1951.)

Neurocidculatory Asthenia

The differential diagnosis between neurocirculatory asthenia and anxiety neurosis is described by the authors. They find in 110 patients that in neurocirculatory asthenia there was a great incidence of sighing, breathlessness, dizziness, paresthesias, chest pain, pain radiating to the left arm, vascular throbbing and effort trouble. In anxiety neurosis sweating, chronic fatigue, depression, apprehension, shaking and bad dreams were prevalent. (H.H. W. Miles and S. Cobb, New Eng. J. of Med., 245:711, Nov. 4, 1951). (H. H. W. Miles and S. Cobb, *New Eng. J. of Med.*, 245: 711, 1951.)

Duuytren's Contracture

The most likely cause of this lesion is repeated minor traumata, perhaps aggravated by a disturbance in the Vitamin E metabolism. In the authors' series the average duration of the condition before treatment was 18 months to 2 years. First noted in most cases were thickening or a nodule in the skin of the palm; however a number of patients felt only stiffness and increasing flexion of the fingers. Slight pain, or numbness and tingling were noted by a minority of the cases. Most cases showed bilateral lesions, although the onset was not observed at the same time in both hands. The treatment is surgical. (J. A. Ross and J. H. Annan. Ann. Surg., 134:186, August 1951.) (J. A. Ross and J. H. Annan. *Ann. Surg.*, 134: 186, 1951.)

Crush Syndrome in Childbirth

Crush syndrome may be a complication of toxemia, premature detachment of the placenta, rupture of the uterus, ectopic pregnancy, or incompatability of transfused blood. The main signs are shock, oliguria or even anuria; the urine contains albumin, casts, many erythrocytes, hemoglobin (and methemoglobin) and creatinine. In severe cases death may supervene even before anuria has developed. The fatality rate of the obstetrical crush syndrome has been estimated as being 50 to 75%; the death occurs most often between the 5th and 9th day of illness. The main anatomical finding is that of a lower nephron nephrosis. (O. Kaser and G. Reichen. *Gynaecologia*, 131: 365, 1951.)

Books On Internal Medicine

A presentation on liver disease[1] is of eminently practical importance. This Ciba symposium comprises all essential phases of this subject, expertly: etiology of liver cirrhosis, etiology and treatment of portal hypertension, protein metabolism, pigment metabolism, infectious liver disease, all topics outlined by scientific leaders in their fields. Another significant comprehensive report on a not less momentous theme, Rheumatic Disease,[2] shows forth all aspects of, and modern approaches to, this widely ramified syndrome. It deals with rheumatic fever, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, with the effect of cortisone and ACTH, gold salts and copper salts, orthopedic and physical management; gout, scleroderma and experimental arthritis are contained in other chapters of this arresting book. A concise treatise on materia medica[3] which stresses practical viewpoints will always be welcomed by the practitioner. The 6th edition of this reputed book gives an instructive introduction into this branch of medicine. The first part outlines elementary materia medica while the following chapters describe the effect and the application of drugs. The last unit of the book sketches briefly the history of materia medica and describes the legal implications. Salt free diet is frequently an indispensable therapeutic tool. The difficulties to maintain a palatable dietary regimen are common knowledge. A practical guide[4] by an experienced dietician will prove to be very helpful.

1. Liver Disease. Consulting Editor Sheila Sherlock, M.D., Editor for the Ciba Foundation. G.E.W. Wolstenholme. M.B. The Blakiston Company. Philadelphia 1951. 249 pages. Cloth. $5.
2. Rheumatic Disease. Based on the Proceedings of the Seventh International Congress of Rheumatic Diseases. Prepared by the Committee on Publications of the American Rheumatic Association, Charles H. Slocum, M.D., Chairman. W. B. Sauders Company, Philadelphia, 1952 449 pages. Cloth. $12.
3. An Introduction to Materia Medica and Pharmacology, by Elsie E. Krug, R.N. and Hugh Alister McGuigan, M.D. Sixth Edition. St. Louis, The C. V. Mosby Company 1951. 612 pages. Cloth. $4.25.
4. Good Food Without Salt. by Margaret Vaughan. Thomas Y. Crowell Company, New York. 1951. 188 pages. Cloth $3.

Notes on MEDICAL STATISTICS

POLIOMYELITIS IN PREGNANCY

In the third trimester of pregnancy women are particularly sensitive to poliomyelitis. 35 percent of pregnant women who contact poliomyelitis had spontaneous abortion. The over-all mortality rate is about 13 percent. (P. Hprn. Ann. West. Med. & Surg. 5:93, Feb. 1951)

NEW PHARMACEUTICAL PRODUCTS

Isolyn: A scored tablet, containing 50 mg. of isonicotinic acid hydrazide.

Used In: Adjunct to treatment of tuberculosis resistant to streptomycin or not responding to previous therapy.

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Sedadrops: A liquid, containing per 10 drops, phenobarbital, ⅛ gr., pentobarbital sodium, 1/16 gr., and homatropine methylbromide, 1/480 gr.

Used in: Management of hyperactive or restless infant or child; regurgitation due to pyloric spasm and other conditions requiring sedation of pediatric patient.

Dosage: For infants up to one year, 4 to 8 drops three times daily. In older children, dosage is adjusted according to age, weight and indications.

Walker Laboratories, Inc., Mount Vernon, New York.

Progesterone-Breon: Aqueous or oil solution of progesterone in two potencies: 10 mg. and 25 mg. per cc.

Used in: Prevention of threatened or habitual abortion; relief of primary dysmenorrhea and postpartum pain; control of certain types of uterine bleeding.

Dosage: Intramuscular injection, as indicated.

George A. Breon and Company, New York 18, New York.

Diminic: A tablet containing pyrilamene maleate, 25 mg., and methapyrilene hydrochloride, 25 mg.

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Ref. 1. Ricketts, W.A.; Carson, R.M. and Saeks, R.R.; Am. J. Obst. and Gynec. 56:955 (1948).
2. Cheval and Hans; Bruxelles Med. 32: 1677 (1950).
3. Paglari, H., Arch. Sci. Med., 89:89-98 (1950).

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